WO 2004/056762
PCT/DK2003/000900

cc: ERO-FBJ-HWD

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

legal opf.

THALSØ-MADSEN, Birgit
Head of Patent Section
Leo Pharma A/S
Industriparken 55
DK-2750 Ballerup
DANEMARK

Date of mailing *(day/month/year)* 08 July 2004 (08.07.2004)	
Applicant's or agent's file reference 637	**IMPORTANT NOTICE**
International application No. PCT/DK2003/000900	International filing date *(day/month/year)* 19 December 2003 (19.12.2003)
Priority date *(day/month/year)* 20 December 2002 (20.12.2002)	
Applicant LEO PHARMA A/S et al	

1. Notice is hereby given that the International Bureau has **communicated**, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

   AU, AZ, BY, CH, CN, CO, DZ, EP, HU, JP, KG, KP, KR, MD, MK, MZ, RU, TM, US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

   AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BZ, CA, CR, CU, CZ, DE, DK, DM, EA, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, KE, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PG, PH, PL, PT, RO, SC, SD, SE, SG, SK, SL, SY, TJ, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-*bis*)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 08 July 2004 (08.07.2004) under No. WO 2004/056762

4. **TIME LIMITS for filing a demand for international preliminary examination and for entry into the national phase**

   The applicable time limit for entering the national phase will, **subject to what is said in the following paragraph,** be **30 MONTHS** from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of **19 months** from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

   In practice, **time limits other than the 30-month time limit** will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For **regular updates on the applicable time limits** (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at http://www.wipo.int/pct/en/index.html.

   For filing a **demand for international preliminary examination**, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

   It is the applicant's **sole responsibility** to monitor all these time limits.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Simin Baharlou
Facsimile No.+41 22 740 14 35	Facsimile No.+41 22 338 71 30

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 637	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DK 03/00900	International filing date *(day/month/year)* 19.12.2003	Priority date *(day/month/year)* 20.12.2002
International Patent Classification (IPC) or both national classification and IPC C07C225/22		
Applicant LEO PHARMA A/S et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.07.2004	22.09.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Romano-Götsch, R Telephone No. +49 89 2399-8874

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK 03/00900

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-47	as originally filed

Claims, Numbers

1-21, 22 (part)	as originally filed
22 (part), 23-31	received on 24.02.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK 03/00900

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 29-30

because:

☒ the said international application, or the said claims Nos. 29-30 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-31
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-31
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-28, 31, (no opinion: 29-30)
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 29-30 are directed to a method of treatment of the animal body, i.e. they contain subject-matter which no International Authority shall be required to examine (Rule 67.1(iv) PCT). Consequently, an opinion in respect to the industrial applicability of said claims is not established in the present Report.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents cited in the application and/or in the ISR are referred to:

D1: WO 01/42189 A (OTTOSEN ERIK RYTTER ;LEO PHARM PROD LTD (DK)) 14 June 2001 (2001-06-14) cited in the application

D2: WO 98/32730 A (OTTOSEN ERIK RYTTER ;RACHLIN SCHNEUR (DK); LEO PHARM PROD LTD (DK)) 30 July 1998 (1998-07-30)cited in the application

D3: WO 02/45752 A (DIDRIKSEN ERIK JOHANNES;GROTH LOTTE ; HEDEMAN HANNE (DK); AAES HEL) 13 June 2002 (2002-06-13)

D4: RYTTER OTTOSEN, ERIK ET AL: "Synthesis and Structure-Activity Relationship of Aminobenzophenones. A Novel Class of p38 MAP Kinase Inhibitors with High Antiinflammatory Activity" J. MED. CHEM., vol. 46, 2003, pages 5651-5662, XP002282566

D5: WO 03/018535 A (HORNEMAN ANNE MARIE ;OTTOSEN ERIK RYTTER (DK); LEO PHARMA AS (DK);) 6 March 2003 (2003-03-06)

Novelty

The presently claimed matter meets the requirements of Art.33(3) PCT because none of D1-D3 discloses the compounds of claims 1-25, a pharmaceutical composition containing them and their use (claims 26-31).

The present application is directed to 4-(phenyl) aminobenzophenones in which the amino group is further substituted by a carbonyloxymethyl ester (see p.2), as summarized below.

D1 discloses (p.2) 4-(phenyl) aminobenzophenones as inhibitors of interleukin IK-1α and tumour necrosis factor TNF-β, which differ from the compounds on file in that amino group is further substituted by R4, R4 being hydrogen,(C1-C6)alkyl, (C2-C6)olefinic group or (C3-C6)monocyclic hydrocarbon.

D2 (p.1) and D3 (pp.5-6) disclose 4-aminobenzophenones wherein the amino group is further substituted by an aminophenyl group and can be further substituted by an alkoxycarbonyl or alkanoyl group.

Inventive Step

The present application meets the requirements of Art. 33(3) PCT.

Departing from D2 or D3 as the closest prior art, the problem to be solved is the provision of novel 4-aminobenzophenone derivatives.

The solution proposed in the application is represented by 4-aminobenzophenone wherein the amino group is substituted by a phenyl and further substituted by a carbamoyloxyalkyl ester.

D2 and D3 teach that the amino group of the 4-aminobenzophenone has to be substituted by an aminophenyl. Furthermore it can be further substituted, for example, by an alkoxycarbonyl.

There is no hint in D2 or D3, alone or combined with D1, that leads to the 4-aminobenzophenone derivatives on file, in which the amino group carries a carbonyloxymethyl ester group and a phenyl group which cannot be substituted by an amino group. It follows that claims 1-31 on file are regarded as inventive (Art.33(3) PCT).

Industrial Applicability

For the assessment of the presently worded claims 29-30 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not regard as industrially applicable claims to the use of a compound in medical treatment, however will allow claims to a known compound for first use in medical treatment and the use of such compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

Documents D4 and D5 have been cited as P-X document in the search report.

Document D4, published on 11-11-03, is directed to 4-(phenyl)aminobenzophenones derivatives which differ from the substituent of the amino group is not a carbonyloxymethyl ester as on file. Thus, D4 is not relevant to the present application.

D5, published on 6-03-2003 and claiming a priority of 8-02-2002, discloses 4-aminobenzophenones derivatives which fall under the scope of the claims on file. For the time being, no investigation on the priority rights of the present application has been carried out.

R_9 represents (C_1-C_3)alkyl, (C_2-C_3)olefinic group, (C_3-C_6)cyclic hydrocarbon group, heterocyclyl, (C_2-C_3)alkynyl, (C_1-C_3)alkyl-(C_3-C_6)cyclic hydrocarbon or (C_1-C_3)alkyl-heterocyclyl, wherein R_9 may optionally be substituted by one or more substituents represented by R_{10};

R_{10} represents fluoro, chloro, hydroxy, trifluoromethyl, amino, (C_1-C_3)alkyl, (C_1-C_3)alkoxy, (C_1-C_3)alkylamino or (C_1-C_3)alkoxycarbonyl;

and pharmaceutically acceptable salts solvates or hydrates thereof.

EPO 24.02.2005 (101)

23. A compound according to claim 1, wherein R_1 is methyl; R_2 is 2-chloro; R_3 is 2-methyl and 4-fluoro, or 2-methyl and 4-bromo; R_4 is hydrogen or 4-chloro;

R_5 and R_6 independently represent hydrogen or (C_1-C_4)alkyl;

R_7 represents (C_1-C_6)alkyl, (C_3-C_6)cyclic hydrocarbon group, (C_2-C_6)olefinic group, heterocyclyl, (C_2-C_6)alkynyl, (C_1-C_6)alkyl-heterocyclyl, (C_1-C_6)alkyl-(C_3-C_6)cyclic hydrocarbon group, (C_2-C_6)olefinic group-heterocyclyl, (C_2-C_6), olefinic group-(C_3-C_6)cyclic hydrocarbon group, (C_2-C_6)alkynyl-heterocyclyl, (C_2-C_6)alkynyl-(C_3-C_6)cyclic hydrocarbon group; and wherein R_7 may optionally be substituted by one or more substituents represented by R_8;

R_8 represents halogen, hydroxy, trifluoromethyl, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkylamino, (C_1-C_6)alkoxycarbonyl, (C_1-C_9)trialkylammonium in association with a pharmaceutically acceptable anion, cyano, -COOH or Y-R_9;

Y represents -O-, -NR_a-, -NR_aC(O)-, -C(O)NR_a-, -C(O)-, -C(O)O-, -OC(O)-, -NR_aC(O)O- or -$O(CH_2CH_2O)_n$- wherein n is 1, 2, 3 or 4, and R_a and R_b both represents hydrogen;

R_9 represents (C_1-C_3)alkyl, (C_2-C_3)olefinic group, (C_3-C_6)cyclic hydrocarbon group, heterocyclyl, (C_2-C_3)alkynyl, (C_1-C_3)alkyl-(C_3-C_6)cyclic hydrocarbon or (C_1-C_3)alkyl-heterocyclyl, wherein R_9 may optionally be substituted by one or more substituents represented by R_{10};

R_{10} represents fluoro, chloro, hydroxy, trifluoromethyl, amino, (C_1-C_3)alkyl, (C_1-C_3)alkoxy, (C_1-C_3)alkylamino or (C_1-C_3)alkoxycarbonyl;

and pharmaceutically acceptable salts solvates or hydrates thereof.

24. A compound according to claim 1, wherein R_1 is methyl; R_2 is 2-chloro; R_3 is 2-methyl and 4-fluoro, or 2-methyl and 4-bromo; R_4 is hydrogen or 4-chloro;

R_5 and R_6 independently represent hydrogen or methyl;

R_7 represents methyl, ethyl, propyl, iso-propyl, butyl, tert-butyl, pentyl, heptyl, nonyl, 2-methyl-propyl, 1-methyl-propyl, 2,2-dimethyl-propyl, cyclopropyl, cyclobutyl, phenyl, ethenyl, propenyl, phenylmethyl, phenyl-1-allyl or 2-, 3- or 4- pyridyl, all of which may be substituted by R_8;

R_8 represents hydroxyl, carboxy;

Y represents –C(O)-O-, , NH-C(O)-O, -O-, -O-C(O)- or $-O(CH_2-CH_2-O)_n-$, n being 3;

R_9 represents methyl, ethyl, tert-butyl or phenylmethyl;

R_{10} represents fluoro, chloro, hydroxy, trifluoromethyl, amino, (C_1-C_3)alkyl, (C_1-C_3)alkoxy, (C_1-C_3)alkylamino or (C_1-C_3)alkoxycarbonyl;

and pharmaceutically acceptable salts, solvates and hydrates thereof.

25. A compound according to claim 1 selected from the group consisting of

Succinic acid benzyl ester 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

Succinic acid mono-{1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl} ester;

Sodium 3-{1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethoxycarbonyl}-propionate;

{2-[2-(2-Methoxy-ethoxy)-ethoxy]-ethoxy}-acetic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

{2-[2-(2-Methoxy-ethoxy)-ethoxy]-ethoxy}-acetic acid 1-{(4-bromo-2-methyl-phenyl)-[3-chloro-4-(2-methyl-benzoyl)-phenyl]-carbamoyloxy}-ethyl ester;

Succinic acid benzyl ester 1-{(4-bromo-2-methyl-phenyl)-[3-chloro-4-(2-methyl-benzoyl)-phenyl]-carbamoyloxy}-ethyl ester;

Succinic acid mono-(1-{(4-bromo-2-methyl-phenyl)-[3-chloro-4-(2-methyl-benzoyl)-phenyl]-carbamoyloxy}-ethyl) ester;

Succinic acid {(4-bromo-2-methyl-phenyl)-[3-chloro-4-(2-methyl-benzoyl)-phenyl]-carbamoyloxy}-methyl ester methyl ester;

Succinic acid benzyl ester {(4-bromo-2-methyl-phenyl)-[3-chloro-4-(2-methyl-benzoyl)-phenyl]-carbamoyloxy}-methyl ester;

Acetic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

Propionic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

Butyric acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

Butyric acid [[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-methyl ester;

Pentanoic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

Hexanoic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

Octanoic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

Decanoic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

Succinic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester ethyl ester;

Methoxy-acetic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

Methoxy-acetic acid [[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-methyl ester;

Butyric acid 1-[[3-chloro-4-(4-chloro-2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

3-Methoxy-propionic acid 1-[[3-chloro-4-(4-chloro-2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

3,3-Dimethyl-butyric acid [[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-methyl ester;

Cyclopropanecarboxylic acid [[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-methyl ester;

Cyclobutanecarboxylic acid [[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-methyl ester;

2-Hydroxy-propionic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

2-Methyl-but-2-enoic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

2-Hydroxy-2-methyl-propionic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

2-Hydroxy-2-methyl-propionic acid 1-[[3-chloro-4-(4-chloro-2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

Isobutyric acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

Isobutyric acid [[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-methyl ester;

2,2-Dimethyl-propionic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

3-Methyl-butyric acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

2-Methyl-butyric acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

Cyclopropanecarboxylic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

Acrylic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

But-2-enoic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

But-2-enoic acid [[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-methyl ester;

Cyclobutanecarboxylic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

3-Methoxy-propionic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

2-Acetoxy-propionic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

2,2-Dimethyl-propionic acid [[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-methyl ester;

3-Phenyl-acrylic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

Benzoic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

Pyridine-2-carboxylic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

Isonicotinic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

Nicotinic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

Nicotinic acid 1-[[3-chloro-4-(4-chloro-2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

2-Hydroxy-benzoic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

Hydroxy-phenyl-acetic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester;

(S)-2-tert-Butoxycarbonylamino-3-hydroxy-propionic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester (diastereomer A); and

(S)-2-tert-Butoxycarbonylamino-3-hydroxy-propionic acid 1-[[3-chloro-4-(2-methyl-benzoyl)-phenyl]-(4-fluoro-2-methyl-phenyl)-carbamoyloxy]-ethyl ester (diastereomer B).

26. A compound according to any of claims 1-25 for use in therapy.

27. A pharmaceutical composition comprising a compound according to any of claims 1-25, optionally together with another therapeutically active compound, and one or more pharmaceutically acceptable carriers or excipients.

28. A formulation according to claim 27, wherein said other therapeutically active compound is selected from the list consisting of glucocorticoids, vitamin D analogues, anti-histamines, platelet activating factor (PAF) antagonists, anticolinergic agents, methyl xanthines, β-adrenergic agents, COX-2 inhibitors, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum cholesterol-reducing agents, retinoids, zinc salts, and salicylazosulfapyridin (Salazopyrin).

29. A method for the treatment of acne, atopic dermatitis, contact dermatitis, psoriasis, asthma, allergy, arthritis, rheumatoid arthritis, spondyloarthritis, gout, atherosclerosis, chronic inflammatory bowel disease, uveitis and septic shock, the method comprising administering to a patient in need thereof an effective amount of a compound according to any of claims 1-25, optionally in combination with another therapeutically active compound.

30. A method according to claim 29, wherein said other therapeutically active compound is selected from the list consisting of glucocorticoids, vitamin D analogues, anti-histamines, platelet activating factor (PAF) antagonists, anticolinergic agents, methyl xanthines, β-adrenergic agents, COX-2 inhibitors, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum cholesterol-reducing agents, retinoids, zinc salts, and salicylazosulfapyridin (Salazopyrin).

31. The use of a compound according to any of claims 1-25 in the manufacture of a medicament for the treatment of acne, atopic dermatitis, contact dermatitis, psoriasis, asthma, allergy, arthritis, rheumatoid arthritis, spondyloarthritis, gout, atherosclerosis, chronic inflammatory bowel disease, uveitis or septic shock.